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“Development, Standardization and Pharmacological Screening of Polyherbal Formulation for Hepatoprotective activity”

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1. Abstract of proposed work plan/ problem:

*Liver is the most vital organ of the body**.** Liver ailments represent a major global health problem. Liver cirrhosis is the ninth leading cause of death in the world.(Kim et al. 2002). Toxic chemicals, xenobiotics, alcohol consumption, malnutrition, anaemia, medications, autoimmune disorders (Marina, 2006), viral infections (hepatitis A, B, C, D, etc.) and microbial infections are harmful and cause damage to the hepatocytes. Liver injury or liver dysfunction is a major health problem that challenges not only health care professionals but also the pharmaceutical industry and drug regulatory agencies. Liver Herbal-based therapeutics for liver disorders has been in use in India for a long time and has been popularized world over by leading pharmaceuticals. Despite the significant popularity of several herbal medicines in general, and for liver diseases in particular, they are still unacceptable treatment modalities for liver diseases. Synthetic drugs exploited in the treatment of liver diseases are incompetent and may sometimes lead to serious side-effects. In this context, herbal therapy has emerged as a proficient approach with good values in treating hepatic diseases. Developing a satisfactory herbal therapy to treat severe liver diseases requires systematic investigation of properties such as antiviral action (Hepatitis B, Hepatitis C), antihepatotoxicity (antioxidants), stimulation of liver regeneration and choleretic activity. Formulation of herbal medicines with standards of safety and efficacy can revitalize treatment of liver disorders. A large number of plants and formulations have been claimed to have Hepatoprotective activity. Nearly 160 Phytoconstituents from 101 plants have been claimed to possess liver protecting activity. In India, more than 87 plants are used in 33 patented and proprietary multi ingredient plant formulations. In spite of the tremendous advances made, no significant and safe Hepatoprotective agents are available in modern therapeutics. The objective of this research work is to perform phytochemical investigation of selected medicinal plants and to develop a standardized Polyherbal formulation for Hepatoprotective activity which is safe and efficient.*

Keywords: Hepatoprotective, Polyherbal formulation, standardization etc.

2. Introduction:

Traditional medicine is a broad term encompassing health practices, approaches, knowledge and beliefs which incorporate herbal, animal and mineral based medicines, spiritual therapies, manual techniques and exercises which are applied singularly or in combination to treat, diagnose and prevent illness or maintain well-being. Today there has been a lot of interest in the traditional medicine for its potential contribution to health care[1].

Ayurveda is one of the traditional medicinal systems known as Ayurvedic Medicine, has Originated in India from thousands of years ago, also known as the "Mother of All Healing".[2]

The philosophy behind Ayurveda is preventing unnecessary suffering and living a long healthy life. Unlike the allopathic medicinal system which uses mainly synthetic chemicals designed for specific target receptors and primarily gives symptomatic relief, Ayurveda involves the use of natural elements to eliminate the root cause of the disease by restoring balance, at the same time create a healthy life-style to prevent the recurrence of imbalance.

"Herbal medicine" is the oldest form of healthcare known to mankind and it is a major component in all indigenous peoples, traditional medicine and it is a common element in Ayurvedic, Homeopathic, Naturopathic and traditional oriental. And these herbal medicines have existed world-wide with long recorded history and used in ancient Chinese, Greek, Egyptian and Indian medicine for various therapeutic purposes.[3]

The World Health Organization (WHO) estimates that 4 billion people, 80% of the world population still rely mainly on traditional medicines for their health care. The subcontinent of India is well-known to be one of the major bio diversity centers with about 45,000 plant species. In India, about 15,000 medicinal plants have been recorded, in which the communities used 7,000-7,500 plants for curing different diseases. In Ayurveda, single or multiple herbs (Polyherbal) are used for the treatment.

Due to the scientific advancement today, more and more pharmacologically active ingredients of the Ayurvedic medicines as well as their usefulness in drug therapy have been identified. Basically, it is the phytochemical constituent in the herbals which lead to the desired healing effect, such as saponins, tannins, alkaloids, alkenyl phenols, flavonoids, terpenoids, phorbol esters and sesquiterpenes lactones.

Historically, the Ayurvedic literature "Sarangdhar Samhita" has highlighted the concept of polyherbalism to achieve greater therapeutic efficacy in this ancient medicinal system Hence

traditional system of Indian medicine chose the plant formulations and combined extracts of plants rather than individual ones**.**

Even though the active phytochemical constituents of individual plants have been well established, they usually present in minute amount and always, they are insufficient to achieve the desirable therapeutic effects. For this, scientific studies have revealed that plants of varying potency when combined in a particular ratio, it will give a better therapeutic effect and reduce the toxicity as compared to individual use of the plant.

It is known that Ayurvedic herbals are prepared in a number of dosage forms, in which mostly all of them are Polyherbal formulation. Due to synergism, polyherbalism confers some benefits not available in single herbal formulation. It is evident that better therapeutic effect can be reached with a single multi-constituent formulation. For this, a lower dose of the herbal preparation would be needed to achieve desirable pharmacological action, thus reducing the risk of deleterious side-effects. Besides, Polyherbal formulations bring to improved convenience for patients by eliminating the need of taking more than one different single herbal formulation at a time, which indirectly leads to better compliance and therapeutic effect. All these benefits have resulted in the popularity of Polyherbal formulation in the market when compared to single herbal formulation.

Due to the fact that Polyherbal formulations are a product of the nature, they are relatively cheaper, eco-friendly and readily available than allopathic drugs. Their better affordability and greater accessibility account for increasing demand globally, especially in rural areas and some developing countries, where costly modern treatments are not available. Moreover, throughout the history, Polyherbal remedies have long stand as traditional beliefs, norms and practices in certain tribes, which are based on centuries' old experience of trials and errors. Put it simply, Polyherbal formulation are more readily acceptable culturally and socially.

Due to all the above reasons: Effectiveness, safety, cheap, ubiquity and better acceptance, made Polyherbal formulation is an ideal treatment of choice, hence higher compliance by the patients and excellent therapeutic effect is ensured.[2]

Many of the Polyherbal formulations have reached widespread acceptability as therapeutic agents for diabetic, arthritics, liver diseases, cough remedies, memory enhancers and adoptogens.

Pharmacological Screening:-

As liver is a vital organ of human body system, because it performs wide range of functions such as detoxification, protein synthesis & production of biochemical's necessary for digestion.

The liver plays a major role in glycogen storage, decomposition of blood cells & plasma protein synthesis. It also produces bile, an alkaline compound which is used in digestion, via the emulsification of lipids. Human can only last up to 24 hours without liver functions. Hence liver is necessary for the survival of human.

There are different types of diseases caused to liver which includes jaundice, acute hepatitis, chronic hepatitis, cirrhosis etc. These diseases are caused due to some factors such as viruses, toxic substances like (allopathic drugs & chemicals) & circulatory disturbances[4].

There are hardly any proven remedies for the prevalent liver disorders among people. No drug has been developed in the modern system of medicine which may stimulate the liver functions & protect it from damage or help in the regeneration of hepatic cells. The only drugs which are available for treatment of liver disorders are corticosteroids and immune-suppressive agents but their use is accompanied by serious side effects. There is an ever-increasing need for an agent which could protect the liver against damages, especially one which facilitate regeneration by proliferation of parenchymatous cells after damage & assists growth of fibrous tissues.

Today, there are thousands year old traditions & records of popular healing methods that have maintained their importance despite new developments & progress in the field of chemistry, pharmaceutics & medicine. Indeed, interest in herbal drugs is increasing. The role of natural products in the development of drugs used in modern medicine is unsurpassed even when synthetic chemistry has been developed beyond expectations[5].

Need for the Study:-

The many species of medicinal plant have been shown to produce beneficial effects in the treatment of various diseases. Historically, plants have been used as folk medicines against various types of diseases. Even today crude extract of medicinal plants are used widely by country to cure human ailments in many countries.

From the literature survey it was found that till date available modern drugs have not been able to come up with a satisfactory answer for liver disorders because of high cost and additional adverse effects. It is therefore necessary to search for alternative drugs for the treatment of liver diseases to replace the currently used drugs of doubtful efficacy and safety. In the absence of reliable modern Hepatoprotective drugs, in allopathic medical practices, herbs play a role in the management of various liver disorders. Numerous medicinal plants and their formulations are used for liver disorders in ethno medical practices and in traditional system of medicine in India. The different plants in the herbal mixture will have different modes of action for curing the disease and in the combined form may sometimes exhibit synergistic activity (enhanced activity than of the individual herbs). Components of the plants, which are not active themselves, can act to improve the stability, solubility and bioavailability or half-life of the active compounds. Hence a particular active principle in the pure form may have only a fraction of the pharmacological activity that it has in its plant matrix, which again highlights the importance in using the plant as a whole or a mixture of plants for treating a diseases. A greater deal of research has been carried out to evaluated scientific basis for the claimed Hepatoprotective activity of herbal agents as single agent or in formulation.

The plant herbal Formulations are developed based on Ayurvedic principles where plants are included for antioxidant activity, Hepatoprotective activity, and specific activity in modulation of different liver disease conditions as many of these herbal ingredients are known to have liver modifying activity. The plants such as *Andrographis paniculata*[6], *Azadirachta indica*[7],*Tinospora cordifolia*[8],*Hibiscus rosa chinensis*[9], *Curcuma longa*[10], *Emblica officinalis*[11], *Moringa oleifera*[12], *Mentha piperita*[13], *Citrus limon*[14], *Trigonella foenum graecum*[15],*and Aloe vera*[16] some additional medicinal plants etc are known traditionally for its effect in jaundice or is found to be protective in liver damage and reported for Hepatoprotective activity. As the individual plants are present in minute amount and insufficient to achieve the desirable therapeutic effects. So from literature survey it is revealed that plants of varying potency when

combined in a particular ratio, Due to synergism effect polyherbalism gives a better therapeutic effect and reduces the toxicity and such type of benefits are not available in single herbal formulation. Hence we have undertaken this study to evaluate the efficacy of the Polyherbal formulation in experimental animals in which acute hepatotoxicity was induced by carbon tetrachloride.[17]

3. Review of Literature and Development in the subject (Previous work done in the Relevant area):

1. Ansar M. Patel et al. (2010)

The researcher studied that Polyherbal formulations Hepjaun syrup **(HA-I)** and Modified Formulations (**HA-II** and **HA-III)**containing aqueous as well as alcoholic extract of crude drugs were evaluated and compared statistically after inducing hepatotoxicity in rats by subcutaneous administration of carbon tetrachloride (CCL4) with olive oil as a diluent in 1:1 %v/v on 2nd and 3rd day. The liver damage was confirmed by estimation of elevated levels of Serum Glutamate Oxaloacetate Transaminase (SGOT), Serum Glutamate Pyruvate Transaminase (SGPT), Alkaline Phosphatase (ALP), serum bilirubin and liver weights. **HA-I, HA-II, HA-III** pre-treatment (500mg/kg) significantly reduces the CCl4 induced elevated serum levels of SGOT, SGPT, SALP and Serum Bilirubin.Therefore, at the end of this study it could be inferred that Polyherbal formulation can be a better and effective for the Hepatoprotective action.

2. P. Bigoniya* and C.S. Singh (2017)

The present study compiled the formulation of Polyherbal liver syrup named "LivPro" was formulated by using lyophilized ethanolic extract of *A. millefolium*, *C. spinosa*, *C. intybus* and *P. kurroa*. Which was standardized by using the guidelines of WHO and Indian Pharmacopoeia followed by in-vivo and in-vitro Hepatoprotective activity in CCl_4 intoxicated rat? Wistar albino rats were treated with vehicle, Silymarin and LivPro (5, 10 and 15 ml/kg) continuously for 14 days. CCl_4 was administered on every alternate day for a week. LivPro showed rich quantity of flavonoids (480 mg/gm), total phenol (396 mg/gm) and alkaloid (103 mg/gm). Treatment with LivPro (10 and 15 ml/kg) resulted in significant normalization ($P<0.01$ to 0.001) of biochemical parameters except albumin. LivPro showed significant elevation ($P<0.001$) of glutathione and reduction ($P<0.001$) in lipid peroxidase enzymes in liver tissue. LivPro (15 ml/kg) treatment showed complete recovery of hepatocytes with reduced vaculation, clear cell lining as well as absence of multinucleated giant cell.

3. P. M. Dandagi et al. (2008),

In this work researcher studied the Polyherbal Suspension formulations F1, F2 and F3 were prepared by using combination of various extracts of *Ferula asafetida*, *Momordica charantia* and *Nardostachys jatamansi* by trituration method were evaluated by carbon tetra

chloride (CCl_4)-induced hepatotoxicity method using Wister rats of either sex. The suspensions were evaluated for the Organoleptic, physicochemical and Hepatoprotective activity. Oral suspensions formulations F3 showed significant Hepatoprotective activity in the order of F3>F2>F1.

4. Arti Gupta, U etal. (2014),

The present work showing that Two Polyherbal tablet formulations were developed by using five bioactive fractionated extracts of *Butea monosperma*, *Bauhinia variegata* and *Ocimum gratissimum* by the wet granulation method and subjected for physicochemical evaluation followed by pharmacological evaluation for hepatoprotective activity using acute liver toxicity model of Paracetamol induced liver damage in rats. The rats were monitored for change in liver morphology, biochemical parameters like serum glutamate pyruvate transaminase (SGPT), serum glutamate oxaloacetate transaminase (SGOT), alkaline phosphatase (ALP) and total bilirubin for Polyherbal tablet formulation at 50 mg/kg and Polyherbal tablet formulation at 100 mg/kg. From the results of biochemical analysis and Histopathological studies, it can be accomplished that Polyherbal tablet formulation at 100 mg/kg can be effectively formulated into a suitable dosage form formulation contains a potent hepatoprotective agent suggested to be a flavone concentrated in Polyherbal formulation which may find clinical application in amelioration of Paracetamol induced liver damage

5. **Vilas A. Arsul etal. (2015),**

Literature survey revealed that phyllanthin and hypophyllanthin from *Phyllanthus niruri*, wedenolactone from *Eclipta alba*, and kutkin from *Picrorhiza kurroa* are responsible for hepatoprotective activity and phenolic and flavonoids are responsible for antioxidant activity. A selected Polyherbal formulation composed of 7 herbal extract mixtures such as Phyllanthus niruri, *Eclipta alba, Cichorium intybus, Boerhaavia diffusa, Embelia ribes, Berberis aristata and Picrorhiza kurroa*. The phytochemical evaluation was carried out by estimation of total phenolic content and total flavonoids. The antioxidant activity was compared with ascorbic acid (ASC) and Rutin as standard. The hepatoprotective activity in carbon tetrachloride induced hepatotoxicity was studied. Assessment of liver function was made by estimating the activities of SGOT, SGPT, ALP, Cholesterol, Bilirubin and Total protein. From the study it is seen that formulation exhibit significant activity.

6. D. Bhattacharyya etal. (2003),

The effect of Himoliv (HV) was evaluated in carbon tetrachloride or Paracetamol induced hepatotoxicity in rats. Liver necrosis was produced by administering single dose of either carbon tetrachloride (CCl4, 1 ml/kg, 50% v/v with olive oil, s.c.) or Paracetamol (PC, 1 g/kg, p.o.). The liver damage was evidenced by elevated levels of serum glutamate oxaloacetate Transaminase (SGOT), serum glutamate pyruvate transaminase (SGPT) and serum alkaline phosphatase (ALP) and hepatic thiobarbituric acid reacting substances (TBARS) and superoxide dismutase (SOD). HV pre-treatment (0.5 and 1.0 ml/kg, p.o.) significantly ($P<0.001$) reduced CCl4 or PC-induced elevations of the levels of SGOT, SGPT, ALP and TBARS, while the reduced concentration of SOD due to CCl4 or PC was reversed. Silymarin (25 mg/kg, p.o.), a known Hepatoprotective drug showed similar results.

7. Tushar Kanti Bera etal. (2011),

This study investigated the Hepatoprotective activity of the Polyherbal formulation Livshis in CCl4-induced hepatotoxic male albino rats. In these antioxidant enzyme activities, such as lipid peroxidation, and liver function test biosensors were assessed. Hepatic antioxidant enzyme activities diminished significantly and hepatic lipid peroxidation Rats were elevated in CCl4-treated animals this study concludes that Livshis is safe for long-term treatment for hepatic protection at doses of 50 mg/kg body weight.

8. S.V. Sureshkumar and S.H. Mishra (2004)

In this work Ethanol extract of Trikatu Churna an Ayurvedic formulation was evaluated for Hepatoprotective activity in rats by inducing liver damage with carbon tetrachloride .the Ethanol extract at an oral dose of 150 mg/kg exhibited a significant protective effect by lowering serum levels of glutamic oxaloacetic Transaminase, alkaline phosphatise and total Bilirubin.

4. Objectives of Research/ Proposed Hypothesis:

Aim: The main purpose of conducting present study is to perform;

"Development, Standardization and Pharmacological Screening of Polyherbal Formulation for Hepatoprotective activity."

Objectives:

- Extraction of dried crude drug powder of Plant material by using suitable Solvents.
- Identification of potential target compounds for present activity from literature survey.
- Development of Polyherbal formulation using selected medicinal plant's active herbal extract with suitable excipients and methods.
- To carry out the standardization of Polyherbal formulation by suitable techniques.
- To perform the stability studies of Polyherbal formulation.
- Evaluation of the Polyherbal formulation for Hepatoprotective activity.
- *In vivo* studies.
- Comparative studies.

5. Methodology to be adopted:

1. Literature survey:-

2. Collection and Authentication of Plant material:-

The plant will be collected from the local Surrounding areas of different districts of Maharashtra and authenticated from Renowned botanist, cleaned, dried and powdered for Further process.

3. Preliminary Phytochemical Screening

A. Extraction of plant material:-

Powdered drug of plant material will be subjected to extraction using different polarity (Non-polar to Polar) Solvents.

B. Preliminary Phytochemical Screening:-

Preliminary Phytochemical Screening of different extracts of selected medicinal plants is carried out to detect various primary and secondary metabolites present within them.

4. Development and standardization of Polyherbal formulation:-

A. Development of Polyherbal formulation will be carried out by using active herbal extract Of selected medicinal plant.

B. Standardization of Polyherbal formulation will be carried out by using evaluation Parameters.

C. Stability Studies of Polyherbal formulation will be carried out by using ICH guidelines.

5. Acute toxicity study:-

The OECD guidelines will be adopted during investigation for determination of safe dose of Polyherbal formulation to perform acute toxicity study.

6. Screening of Hepatoprotective activity of Polyherbal formulation:-

Polyherbal formulation will be subjected to *in vivo* study of Hepatoprotective activity by Comparing with standard using suitable Screening model.

6. Importance of study/ Society application:

International status:

- **US Patent: US 6759061 B2**Liver Function improvement Formulation.
- **US Patent**; **US 6455078 B1**Medicinal herbal composition for treating liver diseases and HIV
- **US Patent**; **US 5693327** Herbal Compositions **.**
- **WO 2011/074001 A2 A** Hepatoprotective Herbal Composition.

National Status:

- Sanjoy Kumar Pal, Yogeshwer Shukla. Herbal Medicine: Current Status and the Future 2003 ;(4):281-288.
- Ansar M. Patel, Snehal S. Darade, Pankaj G. Jain, Ashish M. Kandalkar. Formulation And Evaluation Of Proprietary Polyherbal Formulation For their Hepatoprotective Activity 2010;2(1):305-309.

Significance of the study:

Recently, there is a greater global interest in non-synthetic, natural medicines derived from plant sources due to better tolerance and minimum adverse drug reactions as compared to synthetic medicines. Herbal products are also commonly used by the patients with certain chronic medical conditions, including breast cancer, liver disease, human immunodeficiency, asthma and rheumatologic disorders. WHO estimates that about three-quarters of the worlds Population currently uses herbs and other forms of traditional medicines for the treatment of various diseases. The herbs are formulated in different modern dosage forms, such as Tablets, Capsules, Topical cream, Gel, Ointment and even some novel drug delivery forms, like extended release, sustained release, and microencapsules dosage forms.

Patenting of herbal formulations has increased over the past few years and scientific evidence of therapeutic activity has been reported by performing various *in vitro* and *in vivo* experiments. Herbal formulations are being patented in recent years by various companies and institutes; however the number of patents being filed for herbal or plant origin formulation is Less. The reason for less number of patents is that the herbal formulations need a novelty to obtain a patent, which requires scientific evidence of their pharmacological or pharmacodynamics property against the disease for which they are intended; however most of the companies which market or produce herbal formulations do not have the scientific evidence

of their biological activity and they follow the orally transmitted traditional knowledge rather than the experimental evidence. Recently, some companies and institutes have started generating the proof of biological activity for their herbal formulations by different *in vitro* and *in vivo* experiments to acquire patents. Hence development and scientific studies have validated such herbal medicine or combinations for confirming the biological efficacy and safety which revitalize treatment of liver diseases.

7. Proposed work Plan/ Formulation and Structure of Study: Year-wise Plan of work and Targets to be achieved:

<table>
<tr><th>Sr. No.</th><th>Expected target to be achieved</th><th>1-6 Months</th><th>7-9 Months</th><th>10-12 Months</th><th>13-16 Months</th><th>17-30 Months</th><th>31-33 Months</th><th>34-36 Months</th></tr>
<tr><td>01</td><td>Literature survey</td><td>Literature survey</td><td></td><td></td><td></td><td></td><td></td><td></td></tr>
<tr><td>02</td><td>Collection and authentication of Plant Material</td><td colspan="2">Collection and authentication of Plant Material</td><td></td><td></td><td></td><td></td><td></td></tr>
<tr><td>03</td><td>Extraction, Preliminary Phytochemical Screening of Extracts</td><td colspan="3">Extraction, Preliminary Phytochemical Screening of Extracts</td><td></td><td></td><td></td><td></td></tr>
<tr><td>04</td><td>Development and Standardization and Stability studies of Polyherbal formulation</td><td colspan="4">Development and Standardization and Stability studies of Polyherbal formulation</td><td></td><td></td><td></td></tr>
<tr><td>05</td><td>Acute Toxicity Study</td><td colspan="5">Acute Toxicity Study</td><td></td><td></td></tr>
<tr><td>06</td><td>In vivo Study of Hepatoprotective activity using Animal model by comparing with slandered and it’s Statistical Analysis.</td><td colspan="6">In vivo Study of Hepatoprotective activity using Animal model by comparing with slandered and its Statistical Analysis</td><td></td></tr>
<tr><td>07</td><td>Publishing Research and submitting data</td><td colspan="7">Publishing Research and submitting data</td></tr>
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Future Prospectus / Research Outcomes:-

If promising results from above research study can be obtained along with standardization parameters, stability studies and screening model there may be scope to forward this study from lab scale to large scale up study at industry level by knowing its large scale drying, as well as extraction techniques and equipment's along with additional requirement for getting benefits to the society.

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